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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,418	LE MOUELLIC ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 12/06/07 has been entered. Claims 1-70 and 78-101 are cancelled. Claims 71, 76 and 77 are amended. Claims 71-77 are currently under examination.

This application 10/770,418 filed on Feb. 04, 2004 is a CON of 10/639,754 08/13/2003 which is a CON of 08/466,699 06/06/1995 PAT 6,638,768, which is a CON of 08/301,037 09/06/1994 PAT 6,528,313, which is a CON of 08/048,056 04/19/1993 ABN, which is a CON of 07/598,679 12/19/1990 ABN. Relevant foreign applications are FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 03/20/1989.

Claim objection

1. Claim 77 is objected to because of the following informalities: amended claim 77 is lacking proper punctuation and should include a period at the end of the claim. Appropriate correction is required.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Previous rejection of claims 71-77 as amended remained rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Claims 71, 76 and 77 have been amended and no longer recites "wherein *the expression product* of said DNA construct comprises the second product that confers resistance to selection agent ---". Claims 72-75 depend from claims claim 71.

3. Claims 71-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 12/06/2007 by Applicant.*

Claims 71, 76, and 77 recite the limitation (i) "recombination DNA sequences", and the limitation (ii) "*the* first and second endogenous sequences are *adjacent to* a desired insertion site in the genome of the mammalian cell". Claims 72-75 depend from claim 71.

(i) With regard to the recited "recombination DNA sequences", it is not clear what is encompassed by the term because the term is not defined in the specification and it does not appear to be a term commonly used in the art. The term appears to correspond to the "flanking" sequences disclosed in the specification. It is noted that the term implies that the function of the DNA sequences is in being capable of engaging in recombination. However, it is unclear what the identifying characteristics of the DNA sequences are that are required for the implied function.

(ii) With regard to the limitation "the first and second endogenous sequences are adjacent to a desired insertion site in the genome of the mammalian cell", the specification does not

define the metes and bounds encompassed by the phrase "adjacent to a desired insertion site" in the context of distance constraint for concurrence of homologous recombination between the first recombination DNA sequences and the first endogenous sequences in mammalian genome, and homologous recombination between the second recombination DNA sequences and the second endogenous sequences in mammalian genome. As written, it is unclear whether the limitation "the first and second endogenous sequences are adjacent to a desired insertion site in the genome of the mammalian cell" is meant to imposes any distance limitation between the first and the second endogenous DNA sequences, which are critical for the first and second recited "recombination DNA sequence" to recombine with. In the absence of clear definition of the term "adjacent to a desired insertion site" in the context of homologous recombination, the limitation as written reads on all the DNA sequences of a given chromosome, and the sister chromatins (i.e. duplicated chromosomes) during mitosis and meiosis at the stage of sister chromatin exchange. Accordingly, the metes and bounds of the limitation "the first and second endogenous sequences are adjacent to a desired insertion site in the genome of the mammalian cell" cannot be determined.

With regard to the limitation "the first and second endogenous sequences are *adjacent to* a desired insertion site in the genome of the mammalian cell", the specification does not define the metes and bounds encompassed by the phrase. The term "adjacent" is broad and is not limited to sequences immediately neighboring a target site. Additionally, what is encompassed by the term "target site" is broad in that it may include a single nucleotide wherein a gene is inserted or in the case of a gene replacement, the entire deleted region is the target site. Hence, it is unclear what "the first and second endogenous sequences are adjacent to a desired

insertion site in the genome" encompasses. Claims 71, 76, and 77 recite the limitation "*the* first and second endogenous sequences" in element (A). There is insufficient antecedent basis for this limitation in the claim. Claims 72-75 depend from claim 71.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

4. Claims 71-77 as amended are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* 37 CFR 1.118 (a) states that "No amendment shall introduce **new matter** into the disclosure of an application after the filing date of the application".

In the instant case, the limitation "recombination DNA sequences" recited in claims 71, 76, and 77 is considered as new matter. Claims 72-75 depend from claim 71.

Applicants point to support for the amendments to the claims is found throughout the application as filed, such as at page 4, lines 1-13, which corresponds to paragraphs [0021]-[0023] of US 2004/0203153, publication of instant application, see recitation below.

[0021] The object of the invention is a process for specific replacement, in particular by targeting of a DNA, called *insertion DNA*, constituted by a part of a gene capable of being made functional, or the function of which may be made more effective, when it is recombined with a complementing DNA in order thus to supply a complete recombinant gene in the genome of a eukaryotic cell, characterized in that:

[0022] the site of insertion is located in a selected gene, called the recipient gene, containing the complementing DNA and in that

[0023] eukaryotic cells are transfected with a vector containing an insert itself comprising the insertion DNA and two so-called "flanking" sequences on either side of the DNA of insertions, respectively homologous to two genomic sequences which are adjacent to the desired insertion site in the recipient gene,

There is no explicit recitation of the term "recombination DNA sequence" in the specification of instant application, nevertheless, the term appears to involve certain functionality of the DNA sequences. However, the term "recombination DNA sequence" does not appear to be art recognized term with respect to basic scientific research and potential clinical application of homologous recombination. There is no written description regarding what are the "recombination DNA sequences". In the art, it has been shown that for a DNA sequence to be engaged in homologous recombination, the DNA sequence needs to be recognized by an enzyme, including a specialized endonuclease or topoisomerase-like enzyme, and a double strand DNA break in the DNA sequence is generated by the enzyme. For instance, **Chen et al.,** for instance, reviewed the mechanism gene conversion as one of the two mechanisms of homologous recombination. Chen et al. indicates that the mechanisms of gene conversion involve blunt-ended double-strand break and unidirectional transfer of genetic material from "donor" sequences to a highly homologous "acceptor" (See abstract, Figure 1, Chen et al., Gene conversion: mechanisms, evolution and human disease. *Nat Rev Genet.* 8(10):762-75, 2007). As an additional example, **Cromie et al.** discussed the characteristics of DNA molecules with resected (i.e. with cohesive end) double strand break (DSB) that are required for reciprocal DNA recombination events called crossover (CO) and non-crossover (NCO), and Cos and NCOs arise through different branches of the recombination pathway (See Cromie et al., Branching out:

meiotic recombination and its regulation. *Trends Cell Biol.* 17(9):448-55, 2007). The specification does not describe what characteristics define a "recombination DNA sequence". Accordingly, in the absence of written description of the newly introduced term "recombination DNA sequence" recited in claims 71, 76 and 77, the claims as amended contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 72-75 depend from claim 71.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, and a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the*

disclosure.

Enablement

5. Previous rejection of claims 71-77 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA insertion construct comprising a first DNA sequence and a second DNA sequence, wherein said insertion construct comprises two flanking sequences on either side of the insertion construct respectively homologous to two genomic sequences which are adjacent to a desired insertion site, and wherein said first DNA sequence encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants, and said second DNA sequence encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants, wherein the second DNA sequence is operatively linked to transcriptional and translational regulatory elements and is located downstream of the first DNA sequence, wherein the expression of the second product that confers resistance to a selection agent involved in the selection of transformants, and wherein the first gene product is part or all of a receptor, **does not** reasonably provide enablement for a DNA construct comprising a second DNA that is not operatively linked to transcriptional control elements or for an insertion construct that is not flanked on either side by arms homologous to the site of insertion, is ***withdrawn*** because the claims have been amended.

The Examiner notes that the claim amendments filed on 12/06/2007 have overcome the issues pertaining to the requirement for the second insertion DNA sequence to be operatively to transcriptional and translational regulatory elements, and that an insertion construct is flanked by sequences that are homologous to the site of insertion.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Previous rejection of claims 71 and 72 under 35 U.S.C. 102(b) as being anticipated by Song et al. (Song et al., Accurate modification of a chromosomal plasmid by homologous recombination in human cells. *Proc Natl Acad Sci U S A.* 84(19): 6820-4, 1987, cited in the PTO-892 dated 12/13/2006 by Examiner), is ***withdrawn*** because the claims have been amended. Applicant's arguments filed 12/06/2007 have been fully considered and they are found persuasive.

Applicant's arguments

Applicant argues the following: As amended, the claims recite a "DNA construct for homologous recombination" comprising two compound elements. Element (A) comprises "a first recombination DNA sequence and a second recombination DNA sequence, wherein the first recombination DNA sequence is homologous to a first endogenous sequence in the genome of a mammalian cell, wherein the second recombination DNA sequence is homologous to a second

endogenous sequence in the genome of the mammalian cell, and wherein the first and second endogenous sequences are adjacent to a desired insertion site in the genome of the mammalian cell." Element (B) comprises "a first insertion DNA sequence and a second insertion DNA sequence," which are further defined in the claims. The claims also recite that "the first and second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct."

Applicant further argues that none of the cited references discloses a DNA construct for homologous recombination that comprises elements (A) and (B) as recited in the amended claims, in which "the first and second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct." Therefore, none of the cited references discloses every element of any of the claims and the claims are not anticipated by the references.

Response to Applicant's arguments

The Examiner agrees that Song et al does not teach all the limitation of claim 71. Song et al. does not teach the limitation (i) the first and the second recombination sequences recited in element (A) of claim 71, and the limitation (ii) the first and the second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct, as recited in claim 71.

7. Previous rejection of claim 76 under 35 U.S.C. 102(b) as being anticipated by Chernajovsky et al. (Chernajovsky et al., Efficient constitutive production of human fibroblast

interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984), is ***withdrawn*** because the claim has been amended.

Applicant's arguments are the same as set forth in the section of the rejection of claims 71 and 72 under 35 U.S.C. 102(b) as being anticipated by Song et al. The Examiner agrees that Chernajovsky et al. does not teach all the limitation of claim 76. Chernajovsky et al. does not teach the limitation (i) the first and the second recombination sequences recited in element (A) of claim 76, and the limitation (ii) the first and the second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct, as recited in claim 76.

8. Claim 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Lindenmaier et al. (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by recombination in vivo. *Gene* 39(1): 33-9, 1985), is ***withdrawn*** because the claim has been amended.

Applicant's arguments are the same as set forth in the section of the rejection of claims 71 and 72 under 35 U.S.C. 102(b) as being anticipated by Song et al. The Examiner agrees that Lindenmaier et al., does not teach all the limitation of claim 77. Lindenmaier et al. does not teach the limitation (i) the first and the second recombination sequences recited in element (A) of claim 77, and the limitation (ii) the first and the second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct, as recited in claim 77.

9. Claims 71, 72 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Sleckman et al. (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987), is ***withdrawn*** because the claim has been amended.

Applicant's arguments are the same as set forth in the section of the rejection of claims 71 and 72 under 35 U.S.C. 102(b) as being anticipated by Song et al. The Examiner agrees that Sleckman et al. does not teach all the limitation of claims 71, 72 and 75. Sleckman et al. does not teach the limitation (i) the first and the second recombination sequences recited in element (A) of claim 71, and the limitation (ii) the first and the second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct, as recited in claim 71.

10. Claims 71 and 73 is rejected under 35 U.S.C. 102(b) as being anticipated by Petkovich et al. (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987), is ***withdrawn*** because the claim has been amended.

Applicant's arguments are the same as set forth in the section of the rejection of claims 71 and 72 under 35 U.S.C. 102(b) as being anticipated by Song et al. The Examiner agrees that Petkovich et al. does not teach all the limitation of claims 71 and 73. Petkovich et al. does not teach the limitation (i) the first and the second recombination sequences recited in element (A) of claim 71, and the limitation (ii) the first and the second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct, as recited in claim 71.

11. Claims 71 and 74 is rejected under 35 U.S.C. 102(b) as being anticipated by George et al. (George et al., Receptor density and cAMP accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988) as evidenced by Emorine et al. (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989), is ***withdrawn*** because the claim has been amended.

Applicant's arguments are the same as set forth in the section of the rejection of claims 71 and 72 under 35 U.S.C. 102(b) as being anticipated by Song et al. The Examiner agrees that George et al., does not teach all the limitation of claims 71 and 74. George et al. does not teach (i) the first and the second recombination sequences recited in element (A) of claim 71, and the limitation (ii) the first and the second insertion DNA sequences are located between the first and second recombination DNA sequences in the DNA construct, as recited in claim 71.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The following rejections under 35 U.S.C. 103(a) are necessitated by claim amendments filed on 12/06/2007 by Applicant.

12. Claims 71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987). *This rejection is necessitated by claim amendments filed on 12/06/2007 by Applicant.*

Mansour et al. teaches a construct pINT-2LACZN/TK containing a lacZ gene positioned to create an in-frame fusion with the int-2 protein-coding region. The int-2-lacZ fusion faithfully reproduced the expression pattern of int-2 RNA. Mansour et al. 1990 further teaches that the ability to target reporter genes, such as lacZ, to specific mouse loci, combined with the ability to move the tagged gene into different mutant backgrounds, may provide an ideal approach for analyzing interactions among genes that participate in a developmental network (See abstract, Mansour et al., 1990). The configuration of homology arms flanking LacZ gene and neo resistant gene taught by Mansour et al., 1990 are the same as the elements (A) and (B) recited in claims 71 (See Figure 3, Mansour et al., 1990). Mansour taught use of flanking homology arms to target an insertion into the genome of a cell wherein a first gene, being a reporter gene, and a

second gene, being a selectable marker conferring resistance are placed between the flanking arms. Mansour taught such a construct such that upon insertion, the reporter gene is in operable linkage with the promoter of the target gene and the selectable marker gene is operably linked to a regulatory element that directs expression in transformed cells, as the DNA construct recited in claim 71.

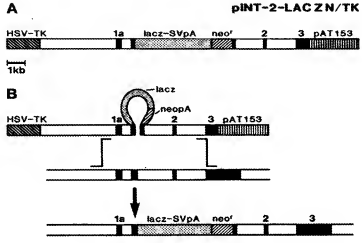

FIG. 3. *int-2–lacZ* targeting vector. (*A*) The closed boxes represent *int-2* exons (22, 23). Open boxes represent introns and noncoding sequences. The hatched boxes represent *neo*^{r} and HSV-tk DNAs as labeled, the stippled box denotes *lacZ* DNA, and the vertically striped box represents plasmid sequences. (*B*) Homologous recombination between the introduced vector DNA (pINT-2-LACZN/TK, upper line) and the endogenous *int-2* locus (middle line) gives rise to a mutant allele (lower line) in which *lacZ* sequences are fused in-frame with *int-2* coding sequences. Shadings are as described for *A*.

Mansour et al. 1990 does not teach (i) the first gene (i.e. targeted locus in mammalian genome) product is part or all of a receptor, as recited in claim 71, and (ii) wherein the receptor is a retinoic acid receptor, as recited in claim 73 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a retinoic acid receptor was known in the art. For instance, Petkovich et al. disclose a cDNA clone

encoding a retinoic acid receptor that binds retinoic acid with high affinity (See abstract, Petkovich et al., 1987).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Mansour et al. 1990 regarding the gene targeting construct comprising a LacZ reporter gene for altering the endogenous genomic copy of the int-2 locus, with the teachings of Petkovich et al. regarding a specific cDNA clone encoding retinoic acid receptor.

One having ordinary skill in the art would have been motivated to substitute LacZ gene in the pINT-2LACZN/TK construct taught by Mansour et al. 1990 with the cDNA clone encoding retinoic acid receptor taught by Petkovich et al. in order to drive the expression of a retinoic acid receptor gene, in target cells using a promoter with known properties and activity, thereby enabling spatial and temporal control over the ectopic expression as Mansour demonstrated for the lacZ gene.

There would have been a reasonable expectation of success given (i) the construct taught by Mansour et al. 1990 can successfully alter gene of interest in a mammalian genome, and (ii) the construct for cDNA clone encoding retinoic acid receptor was readily available by the teachings of Petkovich et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

13. Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous

recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Chernajovsky et al.** (Chernajovsky et al., Efficient constitutive production of human fibroblast interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984). *This rejection is necessitated by claim amendments filed on 12/06/2007 by Applicant.*

The teachings of Mansour et al., 1990 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al., 1990 (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of Petkovich et al., 1987.

Mansour et al. 1990 does not teach (i) the first gene (i.e. targeted locus in mammalian egnome) product is part or all of an interferon, as recited in claim 76 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interferon was known in the art. For instance, Chernajovsky et al. teach the construction of the plasmid pSVEIF, which harbors the interferon β1 (INF- β1) gene (See Figure 1, Chernajovsky et al., 1984).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Mansour et al. 1990 regarding the gene targeting construct comprising a LacZ reporter gene for altering the endogenous genomic copy of the int-2 locus, with the teachings of Chernajovsky et al. regarding a specific cDNA clone encoding interferon β1.

One having ordinary skill in the art would have been motivated to substitute LacZ gene in the pINT-2LACZN/TK construct taught by Mansour et al. 1990 with the cDNA clone encoding interferon β1 taught by Chernajovsky et al. in order to drive the expression of a interferon β1 gene, in target cells using a promoter with known properties and activity, thereby enabling spatial and temporal control over the ectopic expression as Mansour demonstrated for the lacZ gene.

There would have been a reasonable expectation of success given (i) the construct taught by Mansour et al. 1990 can successfully alter gene of interest in a mammalian genome, and (ii) the construct for cDNA clone encoding interferon β1 was readily available by the teachings of Chernajovsky et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

14. Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Lindenmaier et al.** (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by recombination in vivo. *Gene* 39(1): 33-9,1985). *This rejection is necessitated by claim amendments filed on 12/06/2007 by Applicant.*

The teachings of Mansour et al., 1990 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al., 1990 (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous

recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of Petkovich et al., 1987.

Mansour et al. 1990 does not teach (i) the first gene (i.e. targeted locus in mammalian genome) product is part or all of an interleukin, as recited in claim 77 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interleukin was known in the art. For instance, Lindenmaier et al. teach the construction of the plasmid pAN26-IL2, which harbors the interleukin 2 gene (IL2) (See Figure 1, Lindenmaier et al., 1985).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Mansour et al. 1990 regarding the gene targeting construct comprising a LacZ reporter gene for altering the endogenous genomic copy of the int-2 locus, with the teachings of Lindenmaier et al. regarding a specific cDNA clone encoding interleukin 2.

One having ordinary skill in the art would have been motivated to substitute LacZ gene in the pINT-2LACZN/TK construct taught by Mansour et al. 1990 with the cDNA clone encoding interleukin 2 taught by Lindenmaier et al. in order to drive the expression of an interleukin 2 gene, , in target cells using a promoter with known properties and activity, thereby enabling spatial and temporal control over the ectopic expression as Mansour demonstrated for the lacZ gene.

There would have been a reasonable expectation of success given (i) the construct taught by Mansour et al. 1990 can successfully alter gene of interest in a mammalian genome, and (ii)

the construct for cDNA clone encoding interleukin 2 was readily available by the teachings of Lindenmaier et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

15. Claims 71 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of Petkovich et al. (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **George et al.** (George et al., Receptor density and cAMP accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988) and **Emorine et al.** (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989). *This rejection is necessitated by claim amendments filed on 12/06/2007 by Applicant.*

The teachings of Mansour et al. 1990 and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. 1990 and Petkovich et al. 1987.

Mansour et al. 1990 and Petkovich et al 1987 do not teach the receptor is a 3-β adrenergic receptor, as recited in claim 74 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding *part* or all of a 3-β adrenergic receptor, was known in the art. For instance, George et al. disclose a

plasmid pUC13B2AR containing a beta 2-adrenergic receptor (See Material and Methods, page 666, George et al., 1988), and Emorine et al. teach that human beta 3-adrenergic receptor shares 45.5% identical amino acid sequences of human beta 2-adrenergic receptor.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings Mansour et al. 1990 and Petkovich et al. 1987, regarding the gene targeting construct comprising a receptor gene for altering the endogenous genomic copy of the receptor gene, with the combined teachings of George et al. and Emorine et al. regarding a specific cDNA clone encoding part or all of beta 3-adrenergic receptor.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Mansour et al. 1990 and Petkovich et al. 1987 with the teachings of George et al. and Emorine et al. in order to drive the expression of a beta 3-adrenergic receptor gene, in target cells using a promoter with known properties and activity, thereby enabling spatial and temporal control over the ectopic expression as Mansour demonstrated for the lacZ gene.

There would have been a reasonable expectation of success given (i) the construct taught by Mansour et al. 1990 and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, and (ii) the construct for cDNA clone encoding part or all of beta 3-adrenergic receptor was readily available by the combined teachings of George et al. and Emorine et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

16. Claims 71, 72 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of Petkovich et al. (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **Sleckman et al.** (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987). *This rejection is necessitated by claim amendments filed on 12/06/2007 by Applicant.*

The teachings of Mansour et al. 1990 and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. 1990 and Petkovich et al. 1987.

Mansour et al. 1990 and Petkovich et al. 1987 do not teach the receptor is a receptor for infectious agent recited in claim 72, and an HIV receptor recited in claim 75 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a HIV receptor CD4 was known in the art. For instance, Sleckman et al. teach the retroviral vector construction MNST4, which harbors the CD4 gene (the receptor of infectious HIV) (See Figure 1, Sleckman et al., 1987). HIV is an infectious agent (as recited in claim 72) and the CD4 is a cellular receptor of HIV. Through interaction between which HIV envelope protein and CD4 receptor present on cell surface (an HIV receptor as recited in claim 75), the HIV can infect the cell.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings Mansour et al. 1990 and Petkovich et al. 1987, regarding the gene targeting construct comprising a receptor gene for altering the endogenous genomic copy of the receptor gene, with the teachings of Sleckman et al. regarding a specific cDNA clone encoding HIV receptor.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Mansour et al. 1990 and Petkovich et al. 1987 with the teachings of Sleckman et al. in order to drive the expression of a HIV receptor gene, in target cells using a promoter with known properties and activity, thereby enabling spatial and temporal control over the ectopic expression as Mansour demonstrated for the lacZ gene.

There would have been a reasonable expectation of success given (i) the construct taught by Mansour et al. 1990 and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, and (ii) the construct for cDNA clone encoding an HIV receptor CD4 was readily available by the teachings of Sleckman et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Obviousness-type double patenting rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that the Applicant did not address the provisional obviousness-type double patenting rejection in the response filed on 12/06/2007. Thereby, the provisional obviousness-type double patenting rejection is maintained of the record.

17. Claims 71-77 as amended of instant application No. 10/770,418 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 90, 99 and 108 of the other U.S. application of copending application No. 10/639,754. The instant application No. 10/770,418 is a continuation of the copending application No. 10/639,754.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 71-77 of instant application No. 11/115,868 are drawn to a DNA

construct, encoding two distinct gene products, comprising a first DNA sequence and a second DNA sequence, wherein said first DNA sequence comprises a first coding sequence that encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants, and said second DNA sequence comprises a second coding sequence that encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants, wherein the second DNA sequence is downstream of the first DNA sequence, wherein the expression product of said DNA construct comprises the second product that confers resistance to a selection agent involved in the selection of transformants, in functional form, whereas claims 90, 99 and 108 of the other copending U.S. application No. 10/639,754 are drawn to the followings:

(i) A nucleic acid molecule comprising a recombinant recipient gene, wherein the recombinant recipient gene comprises: (A) a first DNA sequence of a recipient gene; (B) a second DNA sequence of the recipient gene, downstream of the first DNA sequence of the recipient gene; and (C) a DNA sequence heterologous with respect to the recipient gene; wherein the heterologous DNA sequence is between the first DNA sequence of the recipient gene and the second DNA sequence of the recipient gene; wherein the heterologous DNA sequence comprises a first insertion DNA sequence and a second insertion DNA sequence; wherein the first insertion DNA sequence comprises a first coding sequence that encodes a first product that is not a marker involved in the selection of cells transformed with said nucleic acid molecule; and wherein the second insertion DNA sequence comprises a second coding sequence that encodes a second product that is a marker involved in the selection of cells transformed with said nucleic acid

molecule, and a promoter allowing the expression of the second product in a cell transformed with said nucleic acid molecule (claim 90);

(ii) A nucleic acid molecule comprising a recombinant recipient gene, wherein the recombinant recipient gene comprises: (A) a first DNA sequence of the recipient gene; (B) a second DNA sequence of the recipient gene, downstream of the first DNA sequence of the recipient gene; and (C) a DNA sequence heterologous with respect to the endogenous recipient gene; wherein the heterologous DNA sequence is between the first DNA sequence of the recipient gene and the second DNA sequence of the recipient gene; wherein the heterologous DNA sequence comprises a first insertion DNA sequence and a second insertion DNA sequence; wherein the first insertion DNA sequence comprises a first coding sequence that encodes a first product that is not a marker involved in the selection of cells transformed with said nucleic acid molecule, and a regulatory sequence for regulating the expression of the first product; and wherein the second insertion DNA sequence comprises a second coding sequence that encodes a second product that is a marker involved in the selection of cells transformed with said nucleic acid molecule, and a promoter allowing the expression of the second product in a cell transformed with said nucleic acid molecule (claim 99); and

(iii) A nucleic acid molecule comprising a recombinant recipient gene, wherein the recombinant recipient gene comprises: (A) a first DNA sequence of the recipient gene; (B) a second DNA sequence of the recipient gene, downstream of the first DNA sequence of the recipient gene; and (C) a DNA sequence heterologous with respect to the endogenous recipient gene; wherein the heterologous DNA sequence is between the first DNA sequence of the recipient gene and the second DNA sequence of the recipient gene; wherein the heterologous

DNA sequence comprises a first insertion DNA sequence and a second insertion DNA sequence; wherein the first insertion DNA sequence comprises a regulatory sequence; and wherein the second insertion DNA sequence comprises a coding sequence that encodes a product that is a marker involved in the selection of cells transformed with said nucleic acid molecule, and a promoter allowing the expression of the product in a cell transformed with said nucleic acid molecule (claim 108).

Applicant did not address the provisional obviousness-type double patenting rejection in the response filed on 12/06/2007.

Conclusion

18. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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